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EDITORIAL COMMENT

Premature Atrial Contractions

A Wolf in Sheep's Clothing?*

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Premature atrial contractions (PACs) have long been considered a benign electrophysiological phenomenon unlikely to result in serious clinical consequence. In 1998, Haïssaguerre et al. (1) challenged this notion by demonstrating that targeted ablation of ectopic atrial activity among patients with atrial fibrillation (AF) reduced arrhythmia recurrence. This finding strongly implicated PACs as the acute trigger for AF initiation among patients previously diagnosed with the arrhythmia. Subsequent studies among patients without known AF identified an association between PACs and incident AF, both in cohorts of patients with recent cryptogenic stroke (2–4) and in the general population (5–7). It is notable that in most of these studies, atrial ectopy emerged as one of the strongest identifiable predictors of incident AF. Indeed, our group (5) recently reported that PAC count alone yields superior AF risk discrimination and enhanced risk reclassification when compared with a previously validated multivariable clinical AF risk model. Taken together, these earlier studies identify atrial ectopy as an important AF risk factor that may play a critical role in disease pathogenesis.

Beyond enhancing our mechanistic construct of AF initiation and perpetuation, the growing body of evidence linking PACs to clinical disease suggests that atrial ectopy may represent a valuable clinical measurement that could change treatment paradigms. If the relationship between PACs and AF is causal, for instance, treatment of atrial ectopy with either pharmacological or catheter-based therapies could provide a primary prevention strategy to reduce incident arrhythmia. Furthermore, it remains possible that patients with multiple stroke risk factors may benefit from anticoagulation in the setting of a high PAC burden to reduce the likelihood of stroke secondary to impending AF. These strategies remain untested, however, and further data are necessary to build support for clinical trials designed to evaluate these novel therapeutic approaches.

In 2010, Binici et al. (6) used 48-hour ambulatory monitoring data from the Copenhagen Holter Study to assess the association between PACs and the outcomes of incident AF, stroke, and death. In this earlier investigation, excessive atrial ectopy was defined as either 30 or more PACs per hour or an episode of 20 or more consecutive PACs (these definitions were derived from the upper decile cutpoints from the overall cohort). Importantly, over a median follow-up of 6.3 years, this study found that excessive atrial ectopy conferred a nearly 3-fold increased risk of AF hospitalization. These investigators also demonstrated that a high PAC burden was associated with a combined endpoint of stroke or death, a finding that persisted in a sensitivity analysis that censored patients at the time of an AF diagnosis. This last observation hinted at the intriguing notion that PACs could be associated with adverse clinical outcomes *independent* of AF.

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In this issue of the *Journal*, Larsen et al. (8) take a second look at the Copenhagen Holter Study data to understand the relationship between atrial ectopy and stroke more clearly. The duration of follow-up

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has lengthened (median follow-up is now 14.4 years) and is accompanied by an increase in clinical events, including stroke diagnoses. Using definitions and methodology similar to those of the previous investigation, excessive atrial ectopy was associated with a doubling in the adjusted risk of stroke (hazard ratio: 2.02; 95% confidence interval: 1.17 to 3.49). Notably, only a minority of the patients with excessive ectopy and stroke (14.3%) had a clinical diagnosis of AF before their cerebrovascular accident. Furthermore, the association between PACs and stroke persisted in sensitivity analyses that censored patients at the time of AF diagnosis or treated AF as a time-varying exposure.

The present investigation has several strengths that should be emphasized. Holter data were obtained in an ambulatory, population-based cohort of participants who were well characterized at baseline. The investigators carefully considered and accounted for potential confounders in their analysis, and they applied appropriate statistical methodology to substantiate their findings. Participants were followed for nearly 15 years, and, impressively, no patients were lost to follow-up. In addition, the primary stroke outcome used a specific definition that included only ischemic events and required computed tomography or magnetic resonance imaging for diagnostic confirmation.

We must also consider limitations that may affect our interpretation of the results. As in all observational studies, residual confounding caused by unmeasured or incompletely characterized covariates could potentially result in bias. In addition, the conclusions of the present study may be less applicable to U.S. patients, who may suffer medical comorbidities at a frequency or severity different from that of their Danish counterparts. As acknowledged by the investigators, the present findings do not establish causality, nor do they definitively implicate atrial ectopy as the primary driver of increased risk of stroke or death. The identification of asymptomatic or paroxysmal AF is difficult and is an important limitation shared by nearly all clinical AF investigations. As such, we cannot exclude that some patients with frequent PACs also had AF before they were enrolled in the study, nor can we be completely assured that patients who experienced stroke or death did not have intervening AF. Finally, the investigators analyzed the variability in atrial ectopy between the first and second 24-h periods of Holter monitoring to argue that this monitoring technique has excellent day-to-day reproducibility in detecting a high ectopic atrial burden. The reproducibility and predictive characteristics of serial ambulatory electrocardiographic monitoring at greater time intervals are less clear, however, and the current results do not inform decisions regarding the utility of repeat monitoring for reassessment of clinical risk.

How then do we interpret these results in the context of the earlier literature? Perhaps the most logical explanation, appropriately mentioned by Larsen et al. (8), is that patients with a high burden of atrial ectopy are more likely to develop subclinical AF, which subsequently leads to stroke. As discussed earlier, the limitations in AF diagnosis make this a strong possibility. Further attempts to clarify this issue would be valuable because it is possible that PAC treatment could prevent AF and subsequent strokes without the attendant risks and costs of anticoagulation therapy. A more controversial explanation of the present study is that frequent ectopy results in atrial myopathy that drives both AF and stroke risk. According to what we call the "atrial myopathy hypothesis," AF would be an epiphenomenon outside the causal pathway between PACs and stroke. In considering this possibility, it is important to remember that both TRENDS and ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) trials (9,10) showed no clear temporal association between AF and stroke outcomes as assessed using implantable cardiac device monitoring. In fact, some study participants had device-documented AF only after their cerebrovascular event. In light of the current investigation, it remains possible that the stroke outcomes observed among these device-monitored patients could be explained by the atrial myopathy hypothesis. Finally, it is important to consider that an unidentified primary process may serve to increase atrial ectopy, AF, and stroke risk through separate mechanisms. For instance, as recognized by the investigators, sleep apnea or left atrial enlargement, or both, could result in heightened atrial ectopy and could also increase stroke risk through an alternative pathological pathway. Such a phenomenon would be important to recognize because treatment of PACs in this situation would not be expected to reduce either AF or stroke outcomes. Because atrial ectopy is strongly correlated with other stroke and AF risk factors, a clinical trial that randomizes patients with frequent ectopy to various PAC reduction treatments offers the best hope of understanding these potentially complex relationships.

Regardless of which of the foregoing explanations is ultimately proven correct, it remains evident that atrial ectopy has an important role in stroke prediction. In this context, it is also worthwhile to consider the absolute risk associated with a high PAC burden.

Among participants in this study with a very high burden of atrial ectopic activity relative to the remainder of the population (the top decile of total or consecutive PAC counts), the risk of stroke was approximately 1 in 5. Although this group certainly represents a high-risk cohort, the majority of participants in the excess ectopy group did not develop the study outcome over the long duration of follow-up.

Mounting evidence continues to implicate the role of PACs in the development of clinical diseases such as atrial fibrillation and stroke, and the hope is that continued research efforts will more clearly delineate the causal pathways responsible for this association. The finding of frequent PACs on ambulatory monitoring should no longer be viewed as a benign and easily dismissible observation. Although the appropriate course of action remains unclear, a high burden of atrial ectopy should raise an eyebrow and heighten clinical concern.

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